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EFFECTS OF CL316,243, A BETA3-ADRENOCEPTOR AGONIST, AND PROSTAGLANDIN E2 ON THE PRIMARY BLADDER AFFERENT ACTIVITY OF THE RAT

Hypothesis / aims of study

It has been suggested that β_3-adrenoceptor (β_3-AR) agonists affect not only the efferent but also the afferent pathways innervating the bladder. In addition, prostaglandin E_2 (PGE_2) causes bladder hyperactivity in conscious rats (1). We investigated the direct effects of a β_3-AR agonist (CL316,243; CL) and PGE_2 on single fiber activities of the primary bladder afferent nerves.

Study design, materials and methods

Female Sprague-Dawley rats were used. Under intraperitoneal urethane anesthesia (1.5 g/kg), for monitoring single unit nerve activity of the primary bladder afferents, fine filaments were dissected from the left L6 dorsal roots and placed across a bipolar electrode. Nerve fibers primarily originating from the bladder were identified by electrical stimulation of the left pelvic nerve and by bladder distension. Nerves of which conduction velocity (CV) is more than 2.5 m/sec were determined as Aδ-fibers and those with less than 2.5 m/sec as C-fibers (2). At the beginning of the experiments, the afferent activity measurements with constant bladder filling were repeated three times and the third measurement served as the control observation. Then, CL (10 μg/kg) or its vehicle was administrated intravenously. Thereafter, 10^{-4} M of PGE_2 or saline was instilled intravesically to obtain another three cycles of investigations (Figure 1). The afferent activity is expressed as a percentage of baseline activity, integrated for the whole filling phase, which is based on pressure and volume. One- and two-way ANOVA followed by Tukey's test was applied for statistical comparisons between groups and between before- and after-CL-administration.

Results

35 single afferent fibers (Aδ-fibers: n=16, CV: 3.95 ± 0.65 m/sec, C-fibers: n=19, CV: 1.32 ± 0.09 m/sec) were isolated from 29 rats.
When bladder was filled with saline- or PGE_2-instillation after CL-administration, bladder compliance did not significantly change from the base-line value although it tended to be increased. In contrast, bladder compliance tended to be decreased by PGE_2-instillation without CL-administration.
The afferent activities of Aδ-fibers in response to saline-instillation significantly decreased after CL-administration (Figures 2, 3A). The inhibitory effect of CL was more pronounced when analyzed based on volume (Figure 3A). After the vehicle-administration, PGE_2-instillation itself did not significantly affect the activities of the Aδ-fibers. However, pretreatment with CL significantly inhibited the activities of the Aδ-fibers even when instilled with PGE_2. The inhibitory effect of CL was not statistically different between the saline- and PGE_2-instillation groups (Figure 3A).
In the C-fibers, the activities in response to bladder distension with saline-instillation were not affected by CL-administration (Figure 3B). After vehicle-administration, the activities of the C-fibers were significantly increased when instilled with PGE_2. Furthermore, these increased responses were inhibited by the pretreatment with CL (Figure 3B).

Interpretation of results

The results of the present study suggest that mechano-sensitive Aδ-fibers were inhibited by CL-administration. However, Aδ-fibers were not affected by intravesical PGE_2.
On the other hand, mechano-sensitive C-fibers were activated by intravesical PGE_2, and this activation was attenuated by CL-administration.

Concluding message

The present results clearly demonstrate that β_3-AR agonists can inhibit Aδ-fibers of the primary bladder afferents in the rat. In addition, β_3-AR agonists can inhibit the activated mechano-sensitive C-fiber response to intravesical PGE_2. These findings may give us a new insight into the mechanism of the possible effect of β_3-AR agonists in the treatment of overactive bladder.

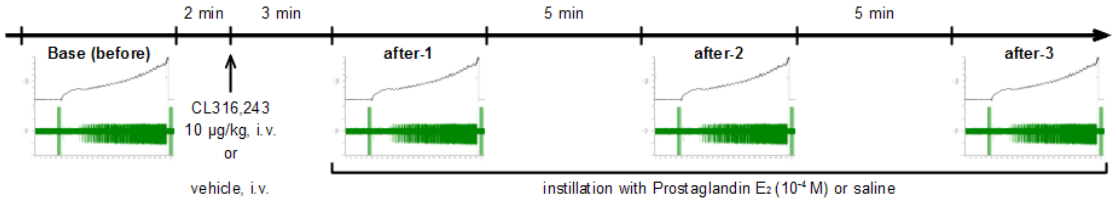

Figure 1. Experimental protocol.

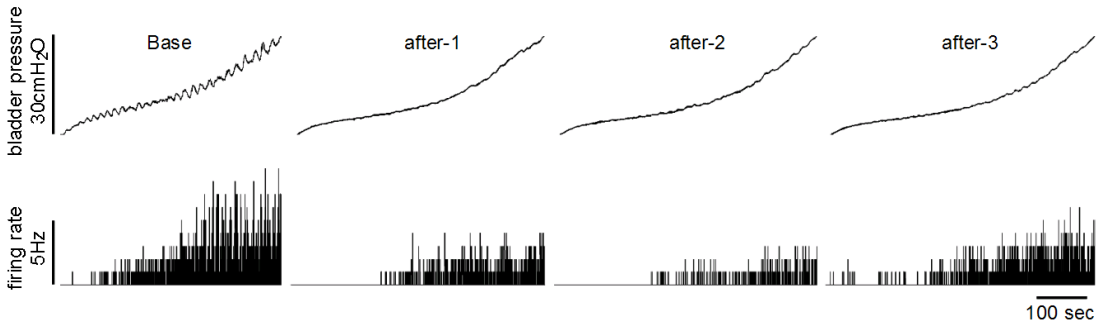

Figure 2. Intravesical pressure (upper tracing) and firing rate (lower tracing) of Aδ-fiber during bladder filling with saline before (Base) and after (-1, -2, -3) CL-administration.

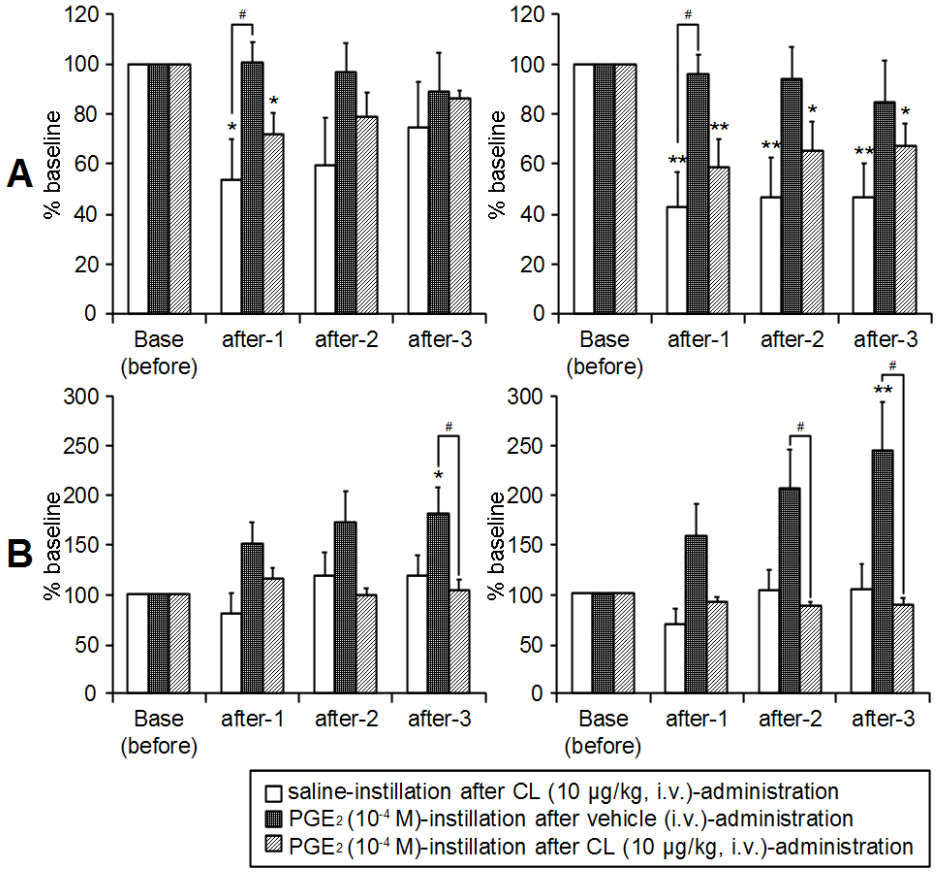

Figure 3. Responses of the Aδ-fibers (A) and C-fibers (B) integrated during the whole filling phase.
Left: based on pressure, Right: based on volume.
**P*<0.05, ***P*<0.01: significant difference Base vs after-1 vs-2 vs -3 (two-way ANOVA followed by Tukey's test).
#*P*<0.05: significant difference between three groups (one-way ANOVA followed by Tukey's test).

References
1. Neurourol Urodyn 2002; 21(6): 558
2. J Neurophysiol 1994; 72: 2420

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Is this a clinical trial?	**No**
What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**Animal Ethics Committee, Shinshu University School of Medicine and Antwerp University Faculty of Medicine.**